UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/982,284	12/01/1997	HENRYK LUBON	030523/0141	9099

7590 10/13/2006

Peter G. Carroll
MEDLEN & CARROLL, LLP
101 Howard Street,
Suite 350
San Francisco, CA 94105

EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/982,284	LUBON ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11-10-06*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *111-124* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *111-124* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendments filed 7-7-05 and 8-19-05 were not entered.

The amendment filed 11-10-05 has been entered.

The arguments filed 8-19-05 appear to correlate to the pending claims and have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-110 have been canceled. Claims 117-124 have been added. Claims 111-124 are pending and under consideration in the instant application.

The effective filing date of the instant invention is 12-1-97.

Claim Rejections - 35 USC ' 112

Written description

Claims 111-116 remain rejected and claims 117-124 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claim 111 is currently limited to a method for secreting protein into urine comprising:

a) providing;

i) a non-human mammal comprising a plurality of urinary tract

cells;

ii) a nucleotide sequence encoding a protein operably linked to a promoter, wherein said promoter is selected from the group consisting of a uromodulin promoter, a uropontin promoter, an osteopontin promoter, and a nephrocalcin promoter;

b) introducing said nucleotide sequence into said urinary tract cells to create a transgenic non-human mammal,

c) expressing said protein in said urinary tract cells under conditions such that said protein is secreted into urine of said transgenic non-human mammal.

Claims 115 is drawn to a non-human transgenic mammal comprising a plurality of urinary tract cells and a nucleotide sequence encoding a protein operably linked to a promoter, wherein said promoter is selected from the group consisting of a whey acidic protein promoter, and a uroplakin promoter.

Claim 117 is similar to claim 111 but is limited to using the uroplakin promoter.

Uromodulin

Yu of record (1994, Gene Expr., Vol. 4, pg 63-75) taught the human, rat and cow uromodulin promoters. Zbikowska of record (Biochem. J. 2002. Vol. 365. pg 7-1 1) taught a 6.72 kb fragment of the human uromodulin gene comprising the 3.7 kb promoter as well as exons 1 and 2 was required to make mice that secreted exogenous proteins into their urine (pg 8, Fig. 1). Therefore, the 6.72 kb fragment of the human uromodulin gene comprising the 3.7 kb promoter and exons 1 and 2 was essential to secrete exogenous proteins into the urine of transgenics. The specification suggests

making a construct for expression in the urinary tract with a 5' regulatory sequence including promoter and enhancer sequences of the uromodulin gene (pg 42, Example 3); however, the specification does not teach the 6.72 kb fragment that is essential to practice the invention. Accordingly, the specification does not provide adequate written description for using a uromodulin promoter to secrete exogenous proteins in the urine of transgenic.

Uropontin

The specification suggests using an uropontin promoter to express exogenous proteins in the urine of transgenics (pg 29, line 26); however, the specification does not provide adequate written description for any uropontin promoter. The NCBI webpage (labeled Entrez Nucleotide and attached hereto) shows a search for uropontin nucleic acid sequences. Only eight uropontin nucleotide sequence are known, none of which are promoters. Therefore, the specification did not provide adequate description of any uropontin promoter. More specifically, the specification does not teach the uropontin promoter required to secrete an exogenous protein into the urine of a transgenic non-human mammal as claimed.

Applicants argue that it is not necessary to understand the mechanism of an invention. Applicants' argument is not persuasive because the structure of a uropontin promoter is absent from the specification and the art at the time of filing. More specifically, a uropontin promoter having the ability to secrete exogenous protein in the urine has not been described.

Osteopontin

The specification suggests using an osteopontin promoter in the claimed invention. Pg 24, lines 6-10, teach:

> "A urinary stone inhibitor protein detected in the cells of the descending limb of the loop of Henle and in papillary surface epithelium at the calyceal fornix, where urine is highly concentrated in stone mineral constituents, was found to be identical to be osteopontin (OPN). OPN mRNA is found at high levels in the kidney, the protein is synthesized and secreted into tubule fluid by the epithelium in the thick ascending loop of Henle and the distal convoluted tubules. Female, pregnant and lactating mice expressed more OPN than males. As animals age, expression is found in more proximal portions. The characterization of osteopontin-k cDNA from bovine renal library showed that it was a kidney cell adhesion molecule of about 261 amino acids and 29.6 Kda molecular weight (Crivello et al., J. Bone Miner. Res. 7: 693-699, 1992).

No one, including Crivello, taught an ostopontin promoter at the time of filing, specifically one capable of expressing exogenous proteins in the urine as claimed. As such, the specification does not provide adequate written description for the osteopontin promoter required to secrete an exogenous protein into the urine of a transgenic non-human mammal as claimed.

Sakuma of record (2003, J Orthop Sci. Vol. 8, pg 361-366) made transgenic mammals comprising a nucleic acid sequence encoding a protein operably linked to a osteopontin 5' regulatory region; however, the fragment of the osteopontin 5' regulatory region used by Sakuma was not known in the art or taught in the specification as originally filed. The osteopontin 5' regulatory region used by Sakuma was not available until 1998 (see pg 361, col. 2, "Production of Transgenic mice" reference 20; Sato).

Applicants argue that it is not necessary to understand the mechanism of an invention. Applicants' argument is not persuasive because the structure of the

osteopontin promoter, specifically the osteopontin promoter having the ability to secrete exogenous protein in the urine, has not been described. Pg 24, lines 10-12, does not teach the structure of any osteopontin promoter. Crivello cited on pg 24 does not teach the structure of any osteopontin promoter.

Nephrocalcin

Debois of record (J. Biol. Chem, 1994, Vol. 269, No. 2, pg 1183-1190) taught the mouse osteocalcin related gene (ORG) was transcribed in mouse kidney and not in bone (pg 1188, col. 1). The specification refers to the ORG gene taught by Debois as the nephrocalcin gene (pg 24, lines 1-5). However, a search for neophrocalcin in the NCBI data base failed to pull up any nucleotide sequences (see Entrez cross-database search). Therefore, reference to the ORG of Debois as the nephrocalcin gene on pg 24 of the specification is a misnomer. Debois taught the 5' non-coding region of ORG; however, it is not readily apparent that the 5' non-coding region of ORG was capable of secreting exogenous protein into urine of transgenics.

Applicants argue pg 23, line 24, through pg 24, line 4, describe the nephrocalcin promoter as being capable of secreting exogenous protein into the urine of transgenic animals. Applicants point to Debois cited above. Applicants argue nephrocalcin is secreted into urine (pg 23, line 25, through pg 24, line 1). Applicants argue that it is not necessary to understand the mechanism of an invention. Applicants' arguments are not persuasive. While Debois taught the osteocalcin related gene (ORG), it is not readily apparent that the ORG correlates to the nephrocalcin gene. More importantly, merely teaching the 5' regulatory region of the ORG and teaching ORG is expressed in kidney

is not adequate written description that the 5' regulatory region of ORG is capable of secreting exogenous protein in the urine of a transgenic as claimed. Paleyanda of record (cited in the discussion of the WAP promoter below) provides evidence that a promoter that causes expression in the kidney may not allow protein expression in the kidney. Applicants have not provide reasonable correlation or evidence that the ORG 5' non-coding region WILL cause exogenous protein to be secreted into the urine as claimed.

WAP promoter

The examiner's position of WAP promoters capable of expressing and secreting exogenous protein into the urine of a transgenic non-human mammal has changed as compared to the final office action sent 3-3-05 in view of applicants' arguments under 102 and 103 and the examiner's further consideration of what was known at the time of filing about the WAP promoter and its ability to express exogenous protein in the kidney or urinary tract cells.

The MGI website states WAP expression is limited to mammary gland and that kidney cells do not express WAP (see MGI webpage labled Gene Expression data for Whey Acidic Protein).

Sympson of record (J. Cell Biol., May 1994, Vol. 125, pg 681-693) taught a transgenic mouse whose genome comprised a sequence encoding stromelysin-I operatively linked to the WAP promoter (page 683 col. 1, 1st ¶). The WAP promoter caused expression of the protein in the milk (bridging pg 683-684) but failed to cause expression in the kidney as determined by RT-PCR (pg 683, col. 2, paragraph 2). Thus,

Sympson establishes that those of skill did not know how to use the WAP promoter of Sympson in a transgenic mammal to cause expression of exogenous protein in the kidney.

Overall, the WAP regulatory region described by Sympson caused expression of exogenous protein in the milk of transgenics but failed to cause expression of exogenous protein in the kidney. Accordingly, the WAP regulatory regions described by Sympson cannot express and secrete exogenous protein into the urine as claimed because it is not capable of causing expression in the kidney.

Paleyanda of record (Transgenic Research, 1994, Vol. 3, pg 335-343) taught making a mouse whose genome comprised a nucleic acid sequence encoding the human protein C operably linked to a 4.1 mouse WAP promoter. hPC RNA expression was observed in the kidney at 0.1% of mammary gland RNA levels in mice from line 4.2.10 (last 5 lines of column 1; Fig. 2). However, Paleyanda failed to detect protein in the kidney (pg 341, second column, lines 5-8). Thus, Paleyanda establishes that those of skill did not know how to use the WAP promoter described by Peyanda to successfully express exogenous protein in the kidney or urine.

Pg 39, Table III, of the instant application shows expression of hPC in the urine of transgenic mice and pigs; however, applicants used the 4.1 kb WAP promoter described by Paleyanda. Pg 36, lines 9-26, teaches:

> "Transgenic mice and pigs were produced containing a transgene composed of a murine whey acidic protein promoter and the human Protein C (HPC) gene. Transgenic pigs containing a transgene composed of the HPC cDNA inserted into the mouse whey acidic protein gene were generated (Velander et al., Proc

> Natl Acad. Sci, 89: 12003-12007, 1992). The promoter is well known and has been used to direct expression and secretion of rHPC into milk in transgenic mammals, as described in, for instance, Paleyanda et al., Transgenic Res. 3: 355-343 (1994), which is incorporated by reference herein in its entirety. The DNA construct comprised a 4.1 kb mouse whey acidic protein (WAP) promoter and a 9 kb HPC gene with 0.4 kb 3' nontranslated sequences (Figure 3A). It was constructed from readily available DNAs using well-known techniques, as described in Drohan et al., Transgenic Res. 3: 355-364 (1994) and Hogan et al., MANIPULATING THE MOUSE EMBRYO, Cold Spring Harbor Press (1986), each of which is incorporated by reference herein in its entirety." (pg 36, lines 9-26)

The specification teaches no more about the 5' regulatory region other than it included the 4.1 kb mouse WAP promoter of Paleyanda, which was described by Paleyanda as being able to express exogenous protein in the kidney according to RT-PCR without being able to detect the exogenous protein in the kidney. The specification does not teach how to overcome the teachings of Paleyanda or discuss this discrepancy. Accordingly, applicants do not adequate written description for the structure of the regulatory region of the transgene or the essential components of the regulatory region required to avoid the failure by Paleyanda.

Niemann of record (Journal of Animal Breeding and Genetics, 1996, Vol. 113, No. 4-5, pg 437-444) taught a transgenic mouse whose genome comprised a sequence encoding Factor VIII operatively linked to the WAP promoter. Niemann taught Factor VIII RNA was detected in mammary glands and kidney (pg 439, Table 1). Niemann states "We have attempted to detect Factor FVIII activity in milk of transgenic mice and sheep by employing ELISA and two different clotting assays. Although we have detected FVIII-mRNA in biopsied mammary gland tissue and milk cells, these methods did not allow reliable detection of FVIII" (pg 441, first full paragraph). Niemann suggests

that the problem may be that the protein is unstable in milk, poorly secreted or that the mRNA is poorly translated. Assuming Niemann failed to secrete Factor VIII into the milk of the transgenics, Niemann also failed to secrete Factor VIII into the kidney of the transgenics. Accordingly, Niemann establishes that those of skill did not know how to use the WAP promoter described by Niemann to successfully express exogenous protein.

The WAP regulatory region described by Niemann failed to provide expression of exogenous protein in the mammary glands. Accordingly, the WAP regulatory region described by Niemann cannot express exogenous protein in the kidney or urine because it failed to cause expression in mammary gland, because Niemann taught the WAP promoter caused 0.1% the amount of expression in kidney cells as compared to mammary gland tissue and because the MGI website taught WAP did not cause expression in the kidney.

Lubon of record taught the WAP promoter allowed secretion of protein into the milk and urine of the transgenic mice and suggested isolating the protein from the milk or urine (US Patent 5,880,327, March 9, 1999; col. 6, lines 45-52; col. 9, line 19). Assuming Lubon did not adequately describe the essential regulatory elements required to use the WAP promoter to secrete exogenous protein into the urine of transgenics, applicants have not provided any additional written description of those essential regulatory elements.

The WAP regulatory element required to overcome the teachings of Sympson, Paleyanda and Niemann to successfully express and secrete exogenous protein in the kidney and urine of a transgenic is essential to practice the claimed invention.

Given that Niemann failed to secrete Factor VIII in the mammary gland of the transgenic mice using the WAP promoter used by applicants, taken with the fact that Paleyanda taught WAP caused 0.1% expression in the kidney as compared to the amount of expression in mammary gland and the fact that the MGI webpage taught WAP did not cause expression in the kidney, the specification fails to adequately describe the WAP regulatory element required to successfully secrete exogenous protein into the kidney or urine of transgenics. It cannot be determined how the WAP promoter described by Niemann that failed to cause protein expression in the milk could have been used by applicants to cause expression in the kidney if WAP causes 0-0.1% less expression in the kidney than in mammary glands. If applicants made structural changes to the promoter of Niemann, such structural changes cannot be envisioned. If the WAP regulatory region used by applicants is identical to the one described by Niemann, the mouse described by Niemann inherently secretes exogenous protein into its urine as claimed.

Since the patent office does not have the ability to determine whether the mice described by Paleyanda failed to secrete hPC into their urine, the following rejection is based on the assumption that the mice described by Paleyanda failed to secrete hPC into their urine. This is a different interpretation of Paleyanda than the 102 rejection, which assumes the mice described by Paleyanda secreted exogenous protein into their

urine. Both interpretations are reasonable given the variable expression results obtained using WAP promoter known in the art and the lack of guidance in the specification.

Accordingly, applicants have not adequately described the regulatory elements essential to use a WAP promoter in transgenics and overcome the teachings in Paleyanda or secrete exogenous protein into the urine. Therefore, transgenic non-human mammals made using the WAP promoter having the ability to secrete exogenous protein into their urine as claimed lack written description.

Accordingly, it is assumed that the lack of expression stromelysin-I under the control of WAP in kidney cells is an indication that stromylysin-I could not have been secreted into the urine and ii) Sympson did not adequately describe the essential regulatory elements required to use the WAP promoter to secrete exogenous protein into the urine of transgenics, the methods and transgenic claimed in the instant application lack written description because applicants have not provided any additional written description of the essential WAP regulatory region required to cause expression and secretion of exogenous protein in the kidney, more specifically into the urine.

Uroplakin promoter

Sun of record taught the uroplakin promoter allowed secretion of protein into the urine of transgenic mice and using the bladder of the mice as a bioreactor for isolating the protein from the urine (WO 96/39494, Dec. 12, 1996; US Patent 5,824,543, Oct. 20, 1998; pg 8, lines 3-12; pg 9, lines 15-36; pg 10, line 4; ¶ bridging col. 5 and 6, col. 6, line 55, Example 2).

The breadth of any uromodulin, osteopontin, etc. promoter as broadly claimed lacks written description

The specification and the art do not provide adequate written description for any uromodulin, uropontin, osteopontin, nephrocalcin, wap or uroplakin promoter as broadly claimed. i.e. "a" uromodulin promoter lacks written description because one uromodulin promoter does not describe all uromodulin genes.

Applicants argue "a" can be singular or plural. Applicants' argument is not persuasive and does not address the basis of the rejection. For some promoters, applicants have not taught the structure of one promoter. Applicants have not taught the structure of more than one uromodulin promoter, more than one uropontin promoter, more than one osteopontin promoter, more than one WAP promoter or more than one uroplakin promoter. Teaching the structure of one human uromodulin promoter for example is not adequate written description for any human uromodulin promoter or any species of uromodulin promoter as broadly claimed.

Expressing and secreting the specific enzymes listed in claims 114, 119 and 123 into the urine of a transgenic non-human mammal

Claims 114, 119 and 123 are directed toward a method of secreting one of numerous specific enzymes into the urine of a transgenic non-human mammal, which remains rejected under written description for reasons of record.

The specification does not provide adequate written description for any transgenics that express and secrete enzymes in their urine. While the specification teaches a number of enzymes in Fig. 7, expression of such enzymes in the urinary tract

of a transgenic mammal may cause an alteration in the phenotype of the mammal. In addition, expression of such enzymes in the urinary tract of a transgenic mammal may cause the enzyme to be non-functional. The specification and the art at the time of filing do not teach transgenics expressing enzymes, specifically protease, glycosyltransferase, phosphorylase, kinase or γ-carboxylase, in the urine. Thus, the specification does not provide adequate written description that the combination of elements described have the desired function, i.e. the transgenics express functional enzyme in their urine or the enzyme alters the phenotype of the transgenic.

Applicants argue enzyme function is not a patentability issue. Applicants argue the claims do not recite a function for the secreted enzyme and that a claim may contain inoperable elements. Applicants' arguments are not persuasive. Applicants have not adequately described the structure of transgenic non-human mammals expressing the specific enzymes listed in claims 114, 119 and 123. Therefore, the method of secreting the enzymes into the urine of the mammal as claimed lacks written description. While non-operative embodiments may be encompassed by claims, the claims cannot specifically recite non-operative embodiments.

New Matter

Claims 111-116 remain and claims 117-124 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection regarding using the uropontin promoter in claim 111 has been withdrawn because the specification suggests using the promoter on pg 29, line 26.

The rejection regarding "human" protein C in claim 112 has been withdrawn in view of applicants' arguments.

The rejection regarding a protein comprising "prothrombin, Factor VII... ...and albumin" in claim 113 has been withdrawn in view of the amendment.

The rejection regarding a protein comprising "phytase, phosphate removing enzyme... ...and phenylacetaldehyde dehydrogenase" in claim 114 has been withdrawn in view of applicants' amendment.

The rejection regarding the concept of claiming the urine of a transgenic mammal as in claim 116 is new matter has been withdrawn in view of applicants' arguments.

The specification as originally filed did not teach or suggest introducing the nucleotide sequence into the urinary tract cells to create a transgenic non-human mammal as broadly encompassed by claims 111 and 115 as amended or claims 117 and 121. The claims encompass injecting DNA into the urinary tract cells of an adult mammal (i.e. gene therapy) to make the mammal "transgenic," which is not contemplated in the specification as originally filed. The specification is limited to introducing a nucleic acid sequence encoding a protein operably linked to a promoter into the genome of the transgenic non-human mammal or providing a transgenic mammal whose genome comprises a nucleic acid sequence encoding a protein operably linked to a promoter.

Applicants argue the claims need not use exact phraseology found in the original specification. Applicants' argument is true but does not apply to this rejection. The breadth of making a transgenic animal using gene therapy as now encompassed by the claim must be supported in the specification as originally filed. However, the concept of making a transgenic mammal using gene therapy now encompassed by the claims was not disclosed or implied in the specification as originally filed.

Applicants argue pg 15, lines 7-20 supports the concepts of gene therapy and the concept of introducing a nucleic acid sequence into a plurality of urinary tract cells as broadly claimed. Applicants' argument is not persuasive. Pg 15, lines 7-20, do not contemplate using gene therapy to make "transgenic animals" as now encompassed by the claims. In context, the cited text is about transgenic non-human mammals whose genomes' comprise a transgene. See pg 15, line 1, which contemplates making a transgenic non-human animal having a transgene stably integrated into their genome. The claims as written are broader than using transgenic non-human mammals having a stably integrated transgene in their genome. As written, the claims require "introducing a nucleotide sequence into urinary tract cells to create a transgenic non-human mammal" and are not limited to using a transgenic non-human mammal whose genome comprises the transgene. The phrase "to create a transgenic non-human mammal" in claims 111, 117 and 121 is an intended use and does not patentable weight because it may not occur. Claim 115 uses "non-human transgenic mammal" in the preamble but does not state the mammal has a transgene stably integrated into its genome. As written, it appears that applicants are claiming that introducing a nucleotide sequence

into urinary tract cells is all that is required "to make a transgenic non-human mammal." As such, the claims are not limited to making a transgenic animal because they do not clearly set forth that a transgenic non-human mammal is made or that the transgenic non-human mammal has the nucleotide sequence incorporated into its genome. Accordingly, the breadth newly claimed is broader than the transgenic non-human mammals originally contemplated in the specification. Pg 15, lines 21-35, also relate to expressing DNA in urinary tract cells and not introducing DNA into urinary tract cells by any means as now broadly claimed.

The specification as originally filed does not contemplate the concept of "a plurality of urinary tract cells" in claim 111. Support for the concept has not been provided and none can be found in the specification as originally filed. Therefore, the phrase is new matter. Pg 15, lines 7-35, are limited to urinary tract cells. Delete "a plurality of" to overcome this rejection.

Enablement

Claims 111-116 remain and claims 117-124 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic non-human mammal whose genome comprises a transgene comprising a nucleic acid sequence encoding a protein operatively linked to a promoter that causes secretion of the protein into the urine of the transgenic mammal, wherein said protein is expressed and secreted into the urine of said transgenic non-human mammal and a method of producing a protein in the urine of said non-human mammal, does not reasonably provide enablement for using a uropontin, osteopontin or WAP promoter to obtain

expression and secretion of exogenous protein in the urine of transgenic non-human mammals or expressing and secreting an enzyme in the urine of transgenic non-human mammals. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

Whey Acidic Protein Promoter

The specification taught making transgenic mice and pigs whose genomes' comprised a sequence encoding human protein C (HPC) operatively linked to the 4.1 kb mouse WAP promoter described by Paleyanda, wherein said mice and pigs expressed HPC in their urine (¶ bridging pg 38-39). However, Paleyanda failed to obtain expression in the kidney using the 4.1 mouse WAP promoter. The specification does not provide adequate guidance for those of skill to overcome the teachings of Paleyanda to obtain HPC expression in the urine. See the written description rejection for the complete discussion of the WAP promoter. The specification does not enable those of skill to overcome the unpredictability established by Sympson, Paleyanda or Niemann to use the WAP promoter in transgenics to express proteins in urine.

Uropontin promoter

While the specification suggests using an uropontin promoter (pg 29, line 26) in the claimed invention, the specification does not provide adequate guidance for one of skill to make a transgenic non-human mammal having a uropontin promoter, specifically where the promoter is capable of secreting an exogenous protein into the urine of the mammal as claimed. The NCBI webpage (labeled Entrez Nucleotide and attached

hereto) shows a search for uropontin nucleic acid sequences. Only four uropontin nucleotide sequence are known, none of which include promoters. Therefore, the specification does not enable those of skill to make the transgenic non-human mammal required in the claims or how to use any such mammal to secrete exogenous proteins into the urine of the mammals as claimed.

Applicants argue methods of making transgenics were well known. Applicants' argument is not persuasive because it does not address the basis of the rejection.

Osteopontin promoter

The specification suggests using an osteopontin promoter in the claimed invention. Pg 24, lines 6-10, teach:

"A urinary stone inhibitor protein detected in the cells of the descending limb of the loop of Henle and in papillary surface epithelium at the calyceal fornix, where urine is highly concentrated in stone mineral constituents, was found to be identical to be osteopontin (OPN). OPN mRNA is found at high levels in the kidney, the protein is synthesized and secreted into tubule fluid by the epithelium in the thick ascending loop of Henle and the distal convoluted tubules. Female, pregnant and lactating mice expressed more OPN than males. As animals age, expression is found in more proximal portions. The characterization of osteopontin-k cDNA from bovine renal library showed that it was a kidney cell adhesion molecule of about 261 amino acids and 29.6 Kda molecular weight (Crivello et al., J. Bone Miner. Res. 7: 693-699, 1992).

No one, including Crivello, taught an ostopontin promoter at the time of filing, specifically one capable of expressing exogenous proteins in the urine as claimed. As

such, the specification does not enable one of skill to make a transgenic non-human mammal using the osteopontin promoter or using the mammal to secrete an exogenous protein into the urine of the mammal as claimed.

Sakuma of record (2003, J Orthop Sci. Vol. 8, pg 361-366) made transgenic mammals comprising a nucleic acid sequence encoding a protein operably linked to a osteopontin 5' regulatory region; however, the fragment of the osteopontin 5' regulatory region used by Sakuma was not known in the art or taught in the specification as originally filed. The osteopontin 5' regulatory region used by Sakuma was not available until 1998 (see pg 361, col. 2, "Production of Transgenic mice" reference 20; Sato). Applicants refer to Jiang (1998) in the arguments on pg 13 of the response filed 10-30-03; however, Jiang did not teach a transgenic mammal as claimed.

Applicants argue methods of making transgenics were well known. Applicants' argument is not persuasive because it does not address the basis of the rejection.

The breadth of any transgenic non-human mammal

Claims 111-124 are not enabled because the specification does not provide adequate guidance for one of skill to make transgenic pigs, sheep, goats, cows, rabbits, or horses. ES cells that provide germline transmission in species other than mice had not been obtained. Furthermore, the parameters required to obtain germline transmission of an exogenous transgene differ between mammalian species for reasons of record. The art at the time the invention was made did not teach how to make a transgenic pig, sheep, goat, cow, rabbit or horse or how to obtain pig, sheep, goat, cow, rabbit or horse ES cells. Therefore, it was unpredictable how to make any transgenic

non-human mammal as broadly claimed at the time the invention was made. The specification does not teach how to make a transgenic pig, sheep, goat, cow, rabbit or horse or how to obtain pig, sheep, goat, cow, rabbit or horse ES cells. Thus, it would have required one of skill undue experimentation to determine how to make a transgenic non-human mammal as broadly claimed.

Applicants arguments point to written description arguments that cannot be found. The written description arguments do not address how make any transgenic non-human mammal as broadly claimed.

Expressing and secreting the specific enzymes listed in claims 114, 119 and 123 into the urine of a transgenic non-human mammal

The specification does not enable expressing specific enzymes in the urine of transgenic mammals (claims 114, 119 and 123). The disclosed purpose of expressing enzymes in the urine of animals is to degrade/detoxify feces, urine, microbes or chemical pollutants. Sympson of record taught expressing stromelysin-1 (which degrades collagen) in transgenic mice and D'Armiento of record taught that transgenic mice expressing MMP (which also degrades collagen) do not survive (page 5734, col. 2, line 6). While the specification teaches a number of enzymes in Fig. 7, expression of such enzymes in the urinary tract of a transgenic mammal may cause an alteration in the phenotype of the mammal. In addition, expression of such enzymes in the urinary tract of a transgenic mammal may cause the enzyme to be non-functional. The specification and the art at the time of filing do not teach transgenics expressing enzymes, specifically protease, glycosyltransferase, phosphorylase, kinase or γ-

carboxylase, in the urine. Given the purpose of the specification taken with the teachings in the specification and in the art, the specification does not enable expressing enzymes in the urine of a transgenic non-human animal. Applicants have not addressed this issue.

Applicants argue enzyme function is not a patentability issue. Applicants' argument is not persuasive. Applicants have not provided adequate guidance for one of skill to use the transgenic non-human mammals expressing the enzymes listed in claims 114, 119 and 123 to degrade/detoxify feces, urine, microbes or chemical pollutants – the sole disclosed purpose for the method claimed. Therefore, the method of secreting the specific enzymes into the urine of the mammal as claimed is not enabled. While non-operative embodiments may be encompassed by claims, the claims cannot specifically recite non-operative embodiments.

Indefiniteness

The rejections of claims 111-116 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention have been withdrawn in view of the amendments.

Claim Rejections - 35 USC § 102

The rejection of claims 111, 113, 115 and 116 under 35 U.S.C. 102(b) as being anticipated by being anticipated by Yull (PNAS, 1995, Vol. 92, pg 10899-10903) as supported by Paleyanda of record (1994, Transgenic Res., Vol. 3, pg 335-343) has been withdrawn in view of applicants' arguments.

The rejection of claims 111, 115 and 116 under 35 U.S.C. 102(b) as being anticipated by being anticipated by Sympson of record (May 1994, J. Cell Biol., Vol. 125, 681-693) for reasons of record in the office action sent 6-25-01, pg 18, as supported by Paleyanda of record (1994, Transgenic Res., Vol. 3, pg 335-343) has been withdrawn. Sympson taught stromelysin-1 protein expression was not detected in the kidney by RT-PCR (pg 683, col. 2, paragraph 2). For art purposes, it is assumed that the WAP promoter used by Sympson cannot cause secretion of exogenous protein into the urine as claimed because Sympson taught RNA encoding the exogenous protein could not be detected in the kidney using RT-PCR.

Claim 115, 121 and 124 are rejected under 35 U.S.C. 102(b) as being anticipated by being anticipated by Nagasawa (Meiji Daigaku Nogakubu Kenkyu Hokoku, 1994, Vol. 100, pg 13-21).

For art purposes, it is assumed that the WAP promoter of Nagasawa is capable of secreting exogenous protein into the urine because the patent office does not have the ability to test the WAP promoter of Nagasawa for its ability to secrete exogenous protein into the urine, because the WAP promoter used by Nagasawa appears to be the same as the one used by applicants and because the specification states the invention includes any WAP promoters without distinguishing the structure of WAP promoters capable of secretion into the urine.

Nagasawa taught a transgenic mouse whose genome comprised a sequence encoding human Growth Hormone operatively linked to the WAP promoter. The WAP promoter inherently caused expression and secretion of human growth hormone in the

urine of the mice as claimed because it has the same structure as the mouse described by applicants, because the WAP promoter was known to cause expression in the kidney (Paleyanda, pg 338, ¶ bridging col. 1-2) and because Example 1 in the specification demonstrates the WAP promoter causes secretion of exogenous protein into the urine. The mouse inherently produced urine as in claim 116 and 124.

Applicants argue Nagasawa did not teach detecting hGH in milk or urine. Therefore, applicants conclude inherency cannot be relied upon. Applicants' argument is not persuasive. First, claim 115 does not require detecting exogenous protein in the urine. Second, applicants' assertion regarding the teachings of Nagaswa are unfounded. Third, the mouse described by Nagasawa inherently secreted and expressed hGH into its urine because it had a WAP promoter – a structure taught by applicants as being part of the invention. For example, example 1 in the specification shows the WAP promoter caused secretion of exogenous protein into the urine. Without evidence to the contrary, the WAP promoter described by Nagasawa was adequate to secrete exogenous protein into the urine as claimed.

Claims 115, 121 and 124 are rejected under 35 U.S.C. 102(b) as being anticipated by being anticipated by Niemann of record (Journal of Animal Breeding and Genetics, 1996, Vol. 113, No. 4-5, pg 437-444).

For art purposes, it is assumed that the WAP promoter of Niemann is capable of secreting exogenous protein into the urine because the patent office does not have the ability to test the WAP promoter of Niemann for its ability to secrete exogenous protein into the urine, because the WAP promoter used by Niemann appears to be the same as

the one used by applicants and because the specification states the invention includes any WAP promoters without distinguishing the structure of WAP promoters capable of secretion into the urine.

Niemann of record (Journal of Animal Breeding and Genetics, 1996, Vol. 113, No. 4-5, pg 437-444) taught a transgenic mouse whose genome comprised a sequence encoding Factor VIII operatively linked to the WAP promoter. Niemann taught Factor VIII RNA was detected in mammary glands and kidney by RT-PCR (pg 439, Table 1). Niemann states "We have attempted to detect Factor FVIII activity in milk of transgenic mice and sheep by employing ELISA and two different clotting assays. Although we have detected FVIII-mRNA in biopsied mammary gland tissue and milk cells, these methods did not allow reliable detection of FVIII" (pg 441, first full paragraph). While Niemann failed to reliably detect FVIII protein and speculates as to why, the WAP regulatory region used by Niemann must cause FVIII protein secretion into the urine because it is the same WAP regulatory region used by applicants. The lack of reliable detection observed by Niemann may have been that the detection method was not sensitive enough. The mouse described by Niemann inherently produced urine (claim 116 and 124).

Applicants argue Niemann did not teach detecting Factor VIII in milk or urine. Applicants point to pg 441, first full paragraph, which states the methods of detecting Factor VIII in the milk are unreliable. Therefore, applicants conclude inherency cannot be relied upon. Applicants' argument is not persuasive. Claim 115 does not require secretion of exogenous protein. In addition, Niemann states expression was detected in

the kidney and mammary gland by RT-PCR. While Niemann states protein detection in the milk was unreliable, Niemann does not state protein secretion did not occur. The citation on pg 441 does not negate the examiner's assertion that the WAP promoter inherently caused secretion of Factor VIII into the urine because the WAP regulatory region used by Niemann is the same as the one used by applicants.

Claims 115, 117 and 120 are rejected under 35 U.S.C. 102(a) as being anticipated by Sun of record (WO 96/93494, Dec. 12, 1996) or 102(e) as being anticipated by Sun of record (US Patent 5,824,543, Oct. 20, 1990).

Sun taught transgenic mice whose genomes' comprised a sequence encoding β-galactosidase operatively linked to the uroplakin promoter, expressing and secreting β-galactosidase in the urine and isolating the protein from the urine (W0 96/93494 – pg 8, lines 3-12; pg 9, lines 15-36; pg 10, line 4; ¶ bridging col. 5 and 6, col. 6, line 55, Example 2; US Patent 5,824,543 - col. 6, lines 5 and 55). The mice inherently produce urine (claim 120).

Applicants argue Sun merely suggests isolating the protein from the urine ("the biological active molecule can be isolated from the urine of these transgenic animals") and concludes the suggestion is inadequate to establish inherency. Applicants' argument is not persuasive. Claims 115 and 117 do not require isolating the protein from the urine. Furthermore, Sun taught isolating the protein from the urine, which is all that is required. Finally, such methods were well-known in the art at the time of filing.

Claims 115, 116, 121, 122, and 124 are rejected under 35 U.S.C. 102(b) as being anticipated by Paleyanda of record (Transgenic Res., 1994, Vol. 3, pg 334-343).

For art purposes, it is assumed that the WAP promoter of Paleyanda is capable of secreting exogenous protein into the urine because the patent office does not have the ability to test the WAP promoter of Paleyanda for its ability to secrete exogenous protein into the urine, because the WAP promoter used by Paleyanda is the same 4.1 kb promoter used by applicants and because the specification does not distinguish the structure of WAP promoters capable of secretion into the urine from those that do not.

Paleyanda taught making a mouse whose genome comprised a nucleic acid sequence encoding the human protein C operably linked to a 4.1 mouse WAP regulatory region. The mouse of Paleyanda inherently secreted hPC into the urine as claimed because hPC RNA expression was observed in the kidney at 0.1% of mammary gland RNA levels in mice from line 4.2.10 as determined by RT-PCR (last 5 lines of column 1; Fig. 2) and because the 4.1 kb mouse WAP promoter used by Paleyanda has the same structure as the 4.1 kb mouse WAP promoter used by applicants (pg 36, lines 14-19). While Paleyanda failed to detect protein in the kidney and speculates as to why (pg 341, second column, lines 5-8), failure to detect protein in the kidney is consistent with hPC being expressed in the kidney as determined by RT-PCR then secreted into the urine of the mice. Accordingly, the mouse described by Paleyanda must have secreted hPC into its urine as claimed because the 4.1 WAP promoter used by Paleyanda is the same one used by applicants and because RT-PCR performed by Paleyanda showed expression in the kidney.

Applicants argue Paleyanda taught hPC was not expressed in the kidney. Applicants argument is not persuasive. While the protein was not detected in the

kidney, the expression product was detected by RT-PCR in the kidney. Failure to detect the protein in the kidney is consistent with hPC being secreted into the urine. The WAP regulatory region used by Paleyanda is the same 4.1 kb region used by applicants; therefore, secretion into the urine must occur as claimed.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on 571-272-0735.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER